

PERSPECTIVE

Is ocular toxoplasmosis caused by prenatal or postnatal infection?

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Ocular toxoplasmosis is commonly attributed to prenatally acquired (congenital) infection unless there is clear evidence that infection was acquired postnatally.^{1–5} We challenge this view by comparing the risks of ocular disease caused by prenatal and postnatal toxoplasmosis. As the history, clinical appearances, and serological findings associated with the two aetiologies are frequently indistinguishable, we summarise the available information on the risks of ocular disease caused by prenatal and postnatal toxoplasmosis. We conclude that there is no evidence to suggest that the majority of cases are the result of prenatal infection. On balance, the available evidence suggests that at least two thirds of ocular toxoplasmosis is caused by postnatal infection. This information is relevant for counselling patients and for the development of strategies to prevent ocular toxoplasmosis.

Natural history of ocular disease caused by prenatal and postnatal toxoplasmosis

Ocular toxoplasmosis is diagnosed in 20–60% of patients with posterior uveitis, most of whom present between 20 and 40 years of age.^{6–11} Although these reports reflect caseloads at referral clinics, the reported age distributions are similar to a recent population based study in the UK. In an active surveillance study of patients with suspected toxoplasmosis seen by ophthalmologists serving a population of seven million, 84 patients were reported over 18 months.¹² Eighty three patients presented aged 10–54 years, with a mean age of 29 years. The incidence of symptomatic ocular toxoplasmosis was 0.4/100 000/year in British born patients and the lifetime risk of disease 18/100 000. Ophthalmologists around the world are faced with similar groups of patients.

AGE AT ONSET OF OCULAR SYMPTOMS AND SIGNS

Age at first occurrence of ocular symptoms is one of the clinical characteristics that might be expected to help distinguish between prenatal and postnatal toxoplasma infection. Evidence from cohort studies of children with prenatal toxoplasmosis show that 20%–80% develop ocular disease, and that the majority of these children have lesions during the first 2 years of life. Four recent, population based, cohort studies^{13–16} of 91 prenatally infected children identified by prenatal or neonatal screening followed children for 1–6 years. Twenty (22%) were found to have retinochoroidal lesions and the proportion in individual studies ranged from 15% to 25%. These findings contrast with the much higher risk of lesions reported in a fifth cohort study conducted 30 years ago¹⁷: 11 prenatally infected children were followed for 20 years and nine (82%) individuals had lesions, five detected during infancy (45%). The difference between the earlier and more recent studies may reflect chance, different definitions of congenital toxoplasmosis, or changes in the natural history

of toxoplasma infection over time. Longer term follow up of more recent cohorts is required to determine whether the majority of individuals infected prenatally will eventually develop eye lesions. However, findings to date suggest that if prenatally infected children do not have lesions in early life, they are unlikely to develop lesions later on. Reports of new lesions in previously unaffected, prenatally infected children are rare and may have resulted from a failure to detect lesions in earlier examinations. Such cases were reported in the following: 1/20 children after 2 years of age in four cohort studies^{13–16}; 3/9 children after 6 years of age by Koppe *et al*¹⁷; 2/54 patients followed for 1–5 years by Mets *et al*¹⁸; 2/37 children after 10 years of age by Peyron *et al*¹⁹; and 2/49 children after 2 years of age and followed for 2–11 years by Couvreur *et al*.²⁰ These studies consistently show that the first appearance of new lesions after 2 years of age in children with no previous lesions is uncommon.

Symptoms of visual impairment are reported infrequently. In some studies, visual loss can be inferred in patients with macular lesions which would be expected to cause some visual loss in the affected eye. In the population based cohort studies,^{13–17} approximately half the patients had reported either unilateral visual impairment or a lesion involving the macula. Visual impairment as a result of these lesions may have been missed in preverbal children, but is likely to have been picked up through visual acuity screening or symptoms during the early school years. Therefore, if current teaching is correct and the majority of toxoplasma retinochoroiditis seen by ophthalmologists is caused by prenatal infection, we would expect 10%–40% of patients (half of the 20%–80% with ocular lesions) to have had symptomatic lesions during childhood.

The age at onset of ocular signs and symptoms due to postnatal toxoplasmosis is more difficult to define. Case reports of postnatally acquired toxoplasmosis show that new lesions can appear for the first time as early as 2 months after the onset of infection²¹ or as late as 5 years.²² A retinochoroidal scar forms after 6–8 weeks.²³ The age at onset of ocular symptoms after postnatal toxoplasmosis is determined by the age specific incidence of postnatally acquired infection and the risk of developing symptomatic lesions. Unfortunately, reliable information on both these factors is lacking. Age specific incidence appears to decrease with age²⁴ and varies between regions. Only two studies, both in atypical settings, have reported on the risk of ocular disease in toxoplasma infected individuals. In one study, 20 patients, who developed retinochoroiditis after a waterborne outbreak of infection, presented to ophthalmologists at a mean age of 56 years (range 15–83 years).² In the second, a population based study in south Brazil, the prevalence of lesions increased from 4% to 25% between 10 and 20 years of age, but no information was given on age at symptomatic presentation.²⁵ In summary, presence

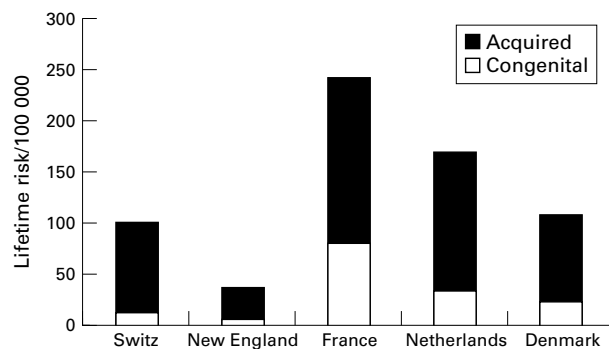


Figure 1 Estimated lifetime risk of ocular disease caused by prenatally and postnatally acquired toxoplasmosis in five countries. Switzerland: birth prevalence of prenatal toxoplasmosis 1.7/10 000; seroprevalence in pregnant women 29%.³⁰ New England, USA: birth prevalence of prenatal toxoplasmosis 0.8/10 000; prevalence of past infection in pregnant women 10%.¹³ France: birth prevalence of prenatal toxoplasmosis 10/10 000, based on incidence of "certain" infection in susceptible pregnant women of 8/1000³¹ and a transmission rate of 29%;³² seroprevalence in pregnant women 54%.³¹ The Netherlands: birth prevalence of prenatal toxoplasmosis 4.3/10 000; prevalence of past infection in pregnant women 45%.¹⁵ Denmark: birth prevalence of prenatal toxoplasmosis 3/10 000; prevalence of past infection in pregnant women 28%.¹⁴

or absence of ocular symptoms in childhood does not differentiate between prenatal or postnatal toxoplasmosis.

OTHER CLINICAL CHARACTERISTICS

In a minority of individuals, other clinical characteristics help to determine whether toxoplasma infection was acquired prenatally or postnatally. For patients with ocular disease and evidence of organ damage in utero or early infancy (such as microphthalmia or a history of intracranial calcification or hydrocephalus in early childhood) the diagnosis of prenatal toxoplasmosis is almost certain. However, such signs are usually asymptomatic and overt neurological symptoms occur in only 1%–3% of infants with prenatal toxoplasmosis.^{13–17} Evidence of retinitis in the absence of a scar in adolescence or adulthood is consistent with postnatal infection as first occurrence of lesions in previously unaffected, prenatally infected individuals is rare. Signs of acute toxoplasmosis, such as lymphadenopathy,¹ further increase the likelihood of postnatal infection.

There is no evidence that other clinical characteristics help to distinguish between prenatal or postnatal infection. Reports of the risk of recurrence of lesions in cohorts of prenatally infected children and case series of patients with postnatal toxoplasmosis appear to be similar (8–40%) but are based on small numbers.^{13 17 21 26} In addition, there is no evidence that patients with bilateral lesions are more likely to have prenatal than postnatal infection. As the risk of bilateral lesions would be expected to increase over time as lesions recur, patients in different studies are most reliably compared at first presentation. Bilateral lesions were reported at presentation by Couvreur and Thulliez in 2/45 patients with postnatal infection,²¹ in one of 20 patients with infection acquired in the Vancouver outbreak,⁷ and in none of the population based cohort studies of 102 prenatally infected children.^{13–17} Higher rates of bilateral lesions are reported in case series of prenatally infected children but these favour inclusion of more severely affected children.^{18–20}

SEROLOGICAL FINDINGS

A further problem is that serological findings rarely provide evidence with which to date infection. Detection of toxoplasma immunoglobulin M (IgM) and IgA antibodies in the first year of life or persistence of IgG beyond 1 year provides clear evidence of prenatal toxoplasmosis. How-

ever, IgM and IgA usually decline to undetectable levels in the first year of life⁴ (p 218) and the presence of IgG in later childhood may be because of prenatal or postnatal infection. Similarly, production of IgM and IgA antibodies after postnatal infection has usually subsided 1 year after infection.⁴ Therefore, most individuals with retinochoroidal lesions due to toxoplasmosis only have detectable IgG antibodies. Furthermore, detection of IgM antibodies in late childhood or adulthood does not necessarily date infection. Persistence or resurgence of IgM antibodies has been reported in prenatal infection²⁷ and is reported to occur in about 5% of postnatally acquired infection⁴ (p 210). Hence, the presence of IgM in adults is more likely to reflect postnatally acquired infection but does not rule out prenatal infection.

Prevalence of clinical and serological findings in practice

In the population based study¹² of patients presenting to ophthalmologists in four UK regions, half reported never having had previous visual symptoms and presented at a mean age of 25 years. Of those with previous symptoms, 2/84 had symptoms in early childhood and no others reported having had symptoms before 10 years of age. Only 5/84 patients had detectable levels of toxoplasma specific IgM, suggesting that infection may have been acquired postnatally. Similarly, other studies rarely report early childhood symptoms or serological evidence of prenatal or postnatal infection in patients with ocular toxoplasmosis.^{28 29}

Risk of ocular toxoplasmosis caused by prenatal and postnatal infection

As few clinical or serological findings distinguish between prenatal or postnatal toxoplasmosis, the ophthalmologist's advice to patients about the origin of their disease should be based on the probability of prenatal or postnatal infection multiplied by the risk of ocular disease in infected individuals over their lifetime.

The lifetime risk of ocular toxoplasmosis as a result of prenatal infection can be estimated by multiplying the birth prevalence of prenatal toxoplasmosis by 80%—the highest estimate of the proportion who will eventually develop ocular lesions.¹⁷ Recent cohort studies in northern Europe and North America give figures for the birth prevalence of prenatal toxoplasmosis ranging from 0.8/10 000 live births in Massachusetts to an estimated 10/10 000 live births in France.^{13 15 16 30–32} Given these figures, the estimated lifetime risk of retinochoroiditis due to prenatal infection in the different centres studied is 6.4–80/100 000 (Fig 1).

Two pieces of information are required to determine the lifetime risk of ocular toxoplasmosis as a result of postnatal infection: the age specific prevalence of toxoplasma infection (we use the prevalence in pregnant women as a proxy measure, Fig 1), multiplied by the risk of retinochoroiditis in individuals with postnatal toxoplasmosis. Several studies have estimated the risk of retinochoroiditis in toxoplasma infected individuals. The lowest estimate is given by Burnett *et al*² who calculated that between 2894 and 7718 individuals acquired infection during the outbreak in greater Victoria, of whom 20 developed toxoplasma retinitis and presented to ophthalmologists: a risk of 0.3%–0.7% in the year after the outbreak. Perkins reported that 1.2% of 1669 patients with postnatally acquired toxoplasmosis identified in case reports developed retinochoroidal lesions and reported a higher risk (2.6%) in patients with neurological or systemic signs and symptoms.¹ The period of follow up was not specified. A population based study in southern Brazil²⁵

showed that approximately 25% of infected adults had retinochoroidal lesions, and 10% developed lesions within 7 years of infection.²⁹ If we use the lowest estimate (0.3%) of the risk of ocular toxoplasmosis in infected individuals given by Burnett *et al.*, and assume no new lesions develop after 1 year post-infection, the estimated lifetime risk of ocular toxoplasmosis due to postnatal infection ranges from 30/100 000 to 160/100 000.

Using these figures, within the centres considered in Figure 1, between 66% and 86% of ocular toxoplasmosis is the result of postnatal infection. This is a conservative estimate as we used the highest reported risk (80%) for retinochoroiditis following prenatal toxoplasmosis, and the lowest reported risk (0.3%) for retinochoroiditis following postnatal infection. Until further research generates more robust estimates, these limited data suggest that at least two thirds of patients with ocular toxoplasmosis acquired the infection postnatally rather than prenatally. These calculations add to arguments, based on clinical and biological findings,³³ that ocular toxoplasmosis caused by postnatal toxoplasmosis is more common than previously suggested.

Conclusion

In summary, the timing of toxoplasma infection leading to ocular disease is rarely known. However, current evidence suggests that many more people are affected by postnatal than by prenatal toxoplasmosis. This has major public health implications. Considerable expertise and expense is concentrated on screening and health information to reduce the risks of toxoplasmosis due to prenatally acquired infection, principally to reduce the risks of ocular morbidity in the long term. Primary preventive strategies should include children and adults at risk of ocular disease as a result of postnatal infection and should not be confined to pregnant women.

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